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Introduction

Multicomponent reactions (MCRs) are typically chemical transformations which yield products in one pot from the structural moieties of three or more reacting components. These types of reactions enable us to synthesize a vast array of structurally diverse compounds in one-step procedures and to introduce cost effective and environmentally friendly synthetic protocols. Hence, MCRs have captivated much attention especially toward the production of heterocyclic compounds.¹⁻³ Methodologies based on MCRs are very useful particularly when they result in the formation of the medicinally privileged heterocyclic scaffolds. Of these heterocyclic compounds, those embedding N-N bonds in their ring systems hold a unique place among a large variety of compounds, and have attracted immense attention because of their valuable pharmacological properties and clinical applications.⁴⁻⁹ Pyrazoles and pyrazole-fused ring systems are recurrent members of this N-heterocyclic family, being found as cores of numerous biologically active compounds.¹⁰⁻¹³ For example, pyrazolo[1,2-b]phthalazines are known for their

Experimental and DFT mechanistic insights into one-pot synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones under catalysis of DBU-based ionic liquids⁺

Sara Fallah-Ghasemi Gildeh, Morteza Mehrdad,* Hossein Roohi, ២ Khatereh Ghauri, Sahar Fallah-Ghasemi Gildeh and Kurosh Rad-Moghadam 咆 *

Benzylation of DBU followed by anion exchange of the resulting salt with trifluoroacetate gave nearly quantitatively the ionic liquid [Bn-DBU][TFA]. It is shown here to be an efficient catalyst for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones *via* the three-component reaction of phthalhydrazide, aromatic aldehydes, and active α -methylene nitriles. DFT calculations at the B3LYP/SVP level and the experimental results are in agreement with a three-step mechanism for this reaction. Based on the DFT calculations, the catalytic effect largely arises from the intrinsic ionic properties of the ionic liquid rather than its action as a simple base. These calculations also predict the existence of two close-in-energy activated complexes whose rate determining roles and energies depend on their interaction with the anionic component of the ionic liquid, as [Bn-DBU][TFA] has shown a higher catalytic activity than [Bn-DBU][OAc]. This mechanistic approach opens up new and promising insights into the rational design of ionic liquid catalysts for the synthesis of 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10-diones. The synthetic method presented here has several prominent advantages.

antihyperglycemic, antibacterial, antiviral, anti-inflammatory, analgesic, antihypoxic, and antipyretic activities.^{14,15} Consequently, many methods have been developed for the synthesis of pyrazolo[1,2-b]phthalazines.¹⁶⁻¹⁸ These involve largely the synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones via the three-component reaction of an aldehyde, phthalhydrazide, and active methylene C-H acid using diverse catalysts such as sulfonated titania-carbon composite C@TiO2-SO3H,¹⁶ Cu(OTf)2,¹⁹ N,N,2,2,6,6-hexamethyl-N-(3-(trimethoxysilyl)propyl)piperidin-4onium iodide grafted onto titania-coated NiFe₂O₄ nanoparticles,²⁰ triethylamine under ultrasonication,¹⁸ L-proline,²¹ zirconium tetrachloride,²² Fe₃O₄ nanoparticles grafted by triethoxy(3-aminopropyl)silane,²³ 2-hydroxyethylammonium acetate,²⁴ N,N,N',N'tetrabromobenzene-1,3-disulfonamide and poly(N-bromo-Nethylbenzene-1,3-disulfonamide),²⁵ β-cyclodextrin,²⁶ H₄W₁₂SiO₄₀ supported on amino-functionalized magnetite nanoparticles,27 $[Bu_3NH][HSO_4]$,²⁸ 1-butyl-3-methylimidazolium hydroxide ([bmim]OH),²⁹ CAN in PEG-400,³⁰ and InCl₃.³¹ However, although many of the recently reported protocols have remarkable merits, some suffer from one or more disadvantages such as harsh reaction conditions, tedious workup procedures, long reaction times, use of metal catalysts, and emission of hazardous materials into the environment. Therefore, there remains room to develop greener, milder, and simpler protocols based on application of retrievable catalysts or solvents such as

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Chemistry Department, University of Guilan, P. O. Box 41335-1914, Rasht, Iran. E-mail: radmm@guilan.ac.ir, m-mehrdad@guilan.ac.ir; Fax: +98 1333367066 † Electronic supplementary information (ESI) available. See DOI: 10.1039/ d0nj03478a

Paper

ionic liquids (ILs) to avoid the emission of hazardous substances into the environment and run the synthesis of phthalazine containing ring systems efficiently. ILs are salts consisting of organic cations and suitable anions, which melt below 100 °C. These low-temperature molten salts have shown interesting properties such as high thermal stability, wide liquid state range, and high solvating capability for a wide range of solutes.³² ILs, irrespective of widespread applications as powerful solvents of both organic and inorganic materials, have found fascinating uses in the last two decades as mild reagents,33 catalysts34-37 and supports of catalysts.³⁸ The evolution of ILs as modern homogeneous catalysts largely arises from the efforts that have been paid to functionalization of their ions with acidic³⁹ and basic⁴⁰ groups, along with scarce studies directed toward employing the intrinsic catalytic activities of their parent ions.⁴¹ ILs, due to their ionic and organic nature, are capable of establishing a wide range of interactions with the reacting solutes including the reaction intermediates and transition states. Thus, depending on the nature of the considered reactions, they may result in significant rate enhancements. The dominant type of interaction between an IL and the reacting species significantly depends on the ions constituting the IL.42 Strongly bound ions in ILs may be unable to approach the substrates due to electrostatic inhibitions.⁴³ Hence, careful selection of ions is crucial to achieve low-melting and catalytically active ionic liquids. Herein is explained the ionic characteristics led to such a selection we made between two DBU-based IL-catalysts used for green and efficient synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-diones via the threecomponent reaction of phthalhydrazide, aromatic aldehydes, and active α -methylene nitriles. However, although a common undetailed mechanism has usually been proposed for this reaction even under various catalytic conditions, no experimental evidence in support of this mechanism was reported. This is due to the fact that no intermediate other than the Knoevenagel condensate of aldehyde and the nitrile can be resolved from the reaction mixtures. In this background, we aimed at studying the details of the mechanism especially under catalysis of two DBU-based ILs by density-functional theory (DFT). As a result, we show that the second intermediate of the reaction has a higher energy and exists between two rate determining activated complexes. This finding indicates why it has not been separated up to now from any reaction mixture. The relative energies of the two activated complexes significantly alters on interaction with the ionic liquids and this encourages the catalyst-designers to consider the ionic properties of ILs beside functionalization of them with acidic and basic groups.

Results and discussion

The DBU-based ILs were prepared *via* benzylation of DBU followed by anion exchange of the resulting product with appropriate salts (Scheme 1). Next, in order to explore the optimal conditions for the synthesis of 3-amino-5,10-dioxo-1-phenyl-5,10dihydro-1*H*-pyrazolo[1,2-*b*]phthalazine-2-carbonitrile **4h** (Table 1), the domino reaction of phthalhydrazide **1**, 4-chlorobenzaldehyde



Scheme 1 Synthesis of the Bn-DBU-based ionic liquids (see S1 of the ESI† for their optimized structures).

2h, and malononitrile was chosen as the model to be examined in different media including the ionic liquid, 8-benzyl-DBU trifluoro-acetate ([Bn-DBU][TFA]), and in different temperatures.

As Table 1 shows, the trial reaction gives negligible yields in the absence of any catalyst at 80 °C (entry 1) or in the presence of [Bn-DBU][TFA] but at room temperature (entry 2). Increasing the amount of [Bn-DBU][TFA] and the reaction temperature lead to significant improvements in the yield of the model product. The best result in terms of the reaction time and the yield was obtained by performing the trial reaction under solvent-free conditions at 100 °C using 28 mol% of the IL (entry 5). Gentle refluxing of the reaction mixture with the IL (28 mol%) in some solvents gave no desirable yields (entries 9-14). It is worth noting that [Bn-DBU][OAc] has not appeared as efficient as [Bn-DBU][TFA] in catalysis of the model reaction (entry 8). Considering that AcO⁻ is a stronger Brønsted base than TFA⁻ ($pK_b = 9.24 vs. 13.77$), the greater catalytic activity of [Bn-DBU][TFA] in comparison with [Bn-DBU][OAc] should arise from a significant interaction it establishes with the reacting species and not from cooperation of TFA and Bn-DBU as two base catalysts. Encouraged by these results, we set out to explore the substrate scope and versatility of the method by employing different arylaldehydes in the reaction with phthalhydrazide 1 and malononitrile or ethyl cyanoacetate 3. Aromatic aldehydes substituted with electron-donating or electronwithdrawing groups react nearly equally well with malononitrile

 Table 1 Optimization of the reaction conditions for the synthesis of 4h^a

ĺ	$ \begin{array}{c} $	2 H + NC	CN Ar = 4-Cl-	$\rightarrow \bigcirc \land $	
Ent.	Catalyst (mol%)	Solvent	Temp. (°C)	Time (min)	Yield ^b (%)
1	_	_	80	60	Trace
2	[Bn-DBU][TFA] (22)	_	r.t.	60	Trace
3	Bn-DBU TFA (22)	_	80	8	65
4	Bn-DBU TFA (22)	_	100	8	71
5	[Bn-DBU][TFA] (28)	_	100	8	90
6	[Bn-DBU][TFA] (28)	—	120	8	89
7	[Bn-DBU][TFA] (39)	—	100	8	90
8	[Bn-DBU][OAc] (28)	—	100	8	76
9	[Bn-DBU][TFA] (28)	H_2O	100	120	NC
10	[Bn-DBU][TFA] (28)	EtOH	80	120	NC
11	[Bn-DBU][TFA] (28)	CH_3OH	60	120	NC
12	[Bn-DBU][TFA] (28)	CH ₃ CN	80	120	NC
13	[Bn-DBU][TFA] (28)	THF	80	120	NC
14	Bn-DBU	DMF	100	120	NC

^{*a*} Reaction conditions: 1 mmol of each reactant in 4 mL of solvent (if used). ^{*b*} Isolated yields. The parameters of the bold entries (5 and 8) were identified as optimal for the applied ILs. NC (not completed).

Table 2	Synthesis of 1H-pyrazolo[1,2-b]phthalazine-5,10-dione	5 4a-4z under the optimal conditions and [Bn-DBU][TFA] catalysis
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		NH NH	+ Ar-CHO + >	<^cn → (
		1 0	2	3	4 0 Ar			
Product	Ar	Х	Time (min)	Yield ^{a} (%)	$\mathrm{TOF}^{b}\left(\mathrm{h}^{-1} ight)$	Mp (°C)	Mp (°C) (lit.)	
4a	4-(NO ₂)-C ₆ H ₄	CN	8	92	24.6	225-227	$(226 - 227)^{16}$	
4b	$3 - (NO_2) - C_6 H_4$	CN	8	93	24.9	267-269	$(269-271)^{40}$	
4c	$2 - (NO_2) - C_6 H_4$	CN	8	92	24.6	265-267	$(265-266)^{18}$	
4d	2-Cl-3-F-C ₆ H ₃	CN	15	76	10.8	269-271	$(266-268)^{41}$	
4e	$4 - F - C_6 H_4$	CN	8	89	23.8	270-271	$(263 - 265)^{18}$	
4f	$3-Br-C_6H_4$	CN	8	90	24.1	260-261	$(262-264)^{43}$	
4g	$4-Br-C_6H_4$	CN	8	91	24.4	269-271	$(270-272)^{43}$	
4ĥ	$4-Cl-C_6H_4$	CN	8	90	24.1	270-272	$(273-276)^{40}$	
4i	$3-Cl-C_6H_4$	CN	8	91	24.4	267-269	$(266-267)^{18}$	
4j	$2-Cl-C_6H_4$	CN	12	89	15.9	259-260	$(258-289)^{16}$	
4k	$2,4-(Cl)_2-C_6H_3$	CN	12	90	16.1	243-245	$(242 - 244)^{44}$	
41	$2 - Me - C_6 H_4$	CN	15	82	11.2	243-245	$(247 - 249)^{42}$	
4m	$4-Me-C_6H_4$	CN	12	86	15.3	235-237	$(236-238)^{40}$	
4n	$4 - N(CH_3)_2 - C_6H_4$	CN	15	87	12.4	232-232	$(230-232)^{45}$	
4o	$4 - MeO - C_6H_4$	CN	12	82	14.6	240-243	$(240-242)^{40}$	
4p	$3-MeO-C_6H_4$	CN	12	87	15.5	265-267	$(264 - 266)^{44}$	
4q	$2-MeO-C_6H_4$	CN	15	88	12.8	155-157	$(154 - 156)^{17}$	
4r	$4-HO-C_6H_4$	CN	12	82	14.6	268-270	$(270-272)^{41}$	
4s	$2-HO-C_6H_4$	CN	15	77	11.0	213-215	$(212-214)^{43}$	
4t	C_6H_5	CN	10	91	19.5	276-278	$(274-276)^{17}$	
4u	$4 - (NO_2) - C_6 H_4$	CO_2Et	18	92	10.9	240-242	$(239-241)^{44}$	
4v	$3 - (NO_2) - C_6 H_4$	CO_2Et	18	90	10.7	235-236	$(236 - 238)^{44}$	
4w	$2 - (NO_2) - C_6 H_4$	CO_2Et	20	89	9.5	233-235	$(235-237)^{18}$	
4x	$4-Br-C_6H_4$	CO_2Et	20	88	9.4	200-202	(205–206) ¹⁸	
4v	$3-Cl-C_6H_4$	CO ₂ Et	18	84	10.0	210-212	$(211-213)^{18}$	
4z	4 -Me- C_6H_4	$\tilde{O_2Et}$	25	87	7.5	202-204	$(201-203)^{44}$	

^{*a*} Yields of the isolated products. ^{*b*} Turnover frequency.Reaction conditions: 1 mmol of each reacting component and 28 mol% of [Bn-DBU][TFA] under solvent-free conditions at 100 °C.

and phthalhydrazide to give 1*H*-pyrazolo[1,2-*b*]phthalazine-5,10dione derivatives (Table 2) in fairly high yields. Similar yields are obtained, however within slightly longer reaction times and with relatively lower turnover frequencies (TOFs), by using ethyl cyanoacetate (X = COOEt) in place of malononitrile (X = CN). These results listed in Table 2 clearly indicate that the reaction can be applied to a wide range of arylaldehydes with different substituents and that the electronic nature of the substituents has no remarkable effect on the yield and rate of the reactions carried out under the optimized conditions. Nevertheless, the arylaldehydes having electron-donating groups on their aromatic rings and those that have steric hindrance due to their *ortho*-substituents react slightly slower than others and give slightly lower yields.

In the next phase of this investigation, we performed DFT (density functional theory) calculations using the B3LYP/SVP^{46,47} level of theory to suggest a reasonable explanation for the efficient catalysis of the reaction by the two ionic liquids and the supremacy of [Bn-DBU][TFA]. These calculations were performed for the first time on the mechanism generally proposed for the reaction in which the three-component synthesis initiates by Knoevenagel condensation of benzaldehyde **2** and malononitrile **3** to give the alkene **5**. Michael addition of this alkene onto phthalhydrazide **1** proceeds *via* the transition state **TS6** and results in formation of the intermediate adduct **6** which subsequently undergoes a Thorpe–Ziegler type cyclization to deliver the product **4t** (Scheme 2).



Scheme 2 A mechanistic proposal for the synthesis of **4**. The optimized structures of the reacting species at the B3LYP/SVP level of DFT in the gas phase are given in Fig. S7 of the ESI.†

However, although there are almost general agreements on the intermediacy of the adduct **6**, it has not yet been isolated from any similar reaction mixture.^{28,48} Moreover, direct application of **5** in place of aldehyde and malononitrile has no effect on the rate of the synthetic reaction. In this background, one may admit that **6** and **4** are the kinetic and the thermodynamic products of the reaction, respectively.

Based on the gas phase DFT calculations, the transition states **TS6** and **TS4** which lead, respectively, to formation of the intermediate **6** and the product **4** are close in Gibbs free energy (Fig. 1). Under these conditions, the intermediate **6** needs about $1.74 \text{ kcal mol}^{-1}$ less Gibbs free energy to dissociate into the



Fig. 1 The energy profile calculated at the B3LYP/SVP level of DFT for the three-component synthesis of **4** in the gaseous phase and absence of IL (black); with the aid of [Bn-DBU][AcO] (trace a, red); and with catalysis of [Bn-DBU][TFA] (trace b, blue). The optimized structures of the above species at the B3LYP/SVP level of theory in the gas phase are given in Fig. S8 of the ESI.†

substrates (1 and 5) than to reach the energy level of TS4 and to form the thermodynamic product 4. These findings delineate pre-equilibrium kinetics for the three-component reaction in which the adduct 6 is formed reversibly by the initial reaction and next undergoes a rate determining reaction to give the product 4. Interestingly, the energy profile significantly alters by addition of the ionic liquids to the reaction mixture in the gaseous phase. Notably, the product 4 gains a considerably higher energy on interaction with either of the two ionic liquids while the energies of the intermediate 6 and the transition states TS6 and TS4 decrease. In the case of binding with [Bn-DBU][OAc], the transition state of the first reaction step, namely TS6a, is more stabilized than that of the second step, namely **TS4a**, so the reaction acquires the energy profile of true pre-equilibrium kinetics in which the rate determining TS4a has a lower energy than under the IL-free conditions.

An important reaction of TS4a and TS4b is the transfer of H₃ to N_5 in 6, which seems to be mediated by delocalization of the π electrons from C=O groups of [OAc]⁻ and [TFA]⁻ anions into the σ^* orbital of the N₁-H₃ bond. As a result, this transfer has low activation energies in the two ILs. The [OAc]⁻ and [TFA]⁻ anions are held in proximity to the dissociating N₁-H₃ bond by a weak H-bond between their O atoms and H₆. The anions not only weaken the original N1-H3 bond but also mediate proton transfer from N1 to N5, accompanied by formation of the pyrazole ring which includes the N1-C5 bond. The DFT calculations also reveal a similar energy profile for the case of using [Bn-DBU][TFA], except that the TS of the first step, namely TS6b, has a higher energy than that of the second step, namely TS4b, and is the rate determinant of the reaction. In other words, the energy required for production of the intermediate 6 is sufficient to convert it into the product 4. In practice, the model reaction in [Bn-DBU] [TFA] is slightly faster than in [Bn-DBU]-[OAc] and this fact lends credit to the DFT calculations. The different efficiencies of the two ILs can be referred to the DFT calculations that estimate the ionic bond of [Bn-DBU]⁺ with $[OAc]^{-}$ about 10.53 kcal mol⁻¹ more stronger than with $[TFA]^{-}$. Moreover, based on these calculations, [OAc]⁻ takes an orientation orthogonal to the averaged plane of [Bn-DBU]⁺, while [TFA]⁻ lies side by side on this plane. In [TFA]⁻, the electronegative fluorine atoms cause the negative charge to be distributed over all the hetero atoms, so it behaves, unlike [OAc]⁻, as a soft anion with no preferred orientation to approach [Bn-DBU]⁺. Consequently, [TFA]⁻ is loosely bound to [Bn-DBU]⁺ and is more available than [OAc]⁻ to form a complex, namely 1b, with phthalhydrazide by H-bonding. Thus, 5 can push away $[Bn-DBU]^+$ more easily from **1b** than from **1a** (the complex of **1** and [Bn-DBU][OAc]) to approach the phthalhydrazide during the Michael addition reaction (Scheme 3).

A comparison between the catalytic efficiency of [Bn-DBU][TFA] and some previously reported catalysts for the synthesis of **4h** is seen in Table 3. As this table shows, most of the reported catalysts need longer times (entries 1, 4, 5, 7, 8, 11 and 12) to give comparable yields of **4h**. Some catalysts are expensive and cannot be prepared conveniently (entries 1, 3, 6 and 9) and some others are made of heavy metals (entries 5, 12, 13) or cannot be separated easily from the reaction mixtures (entries 2, 4 and 8). Notably, [Bn-DBU][TFA] is mildly basic and reasonably amenable to



Scheme 3 The approach of 5 to phthalhydrazide in its complexes with [Bn-DBU][AcO] (1a) and [Bn-DBU][TFA] (1b). The optimized structures at the B3LYP/SVP level of theory in the gas phase are given in Fig. S9 of the ESI.†

Table 3 Comparative catalytic efficiency of [Bn-DBU][TFA] and some previously reported catalysts in the model synthesis of 4h

Ent.	Catalyst ^{Ref.}	Amount of catalyst ^a	Conditions	Time (min)	Yield (%)
1	C@TiO ₂ -SO ₃ H ¹⁶	2.7 mol%	H ₂ O, 100 °C	900	92
2	Et ₃ N ¹⁸	20 mol%	EtOH, ultrasonication	60	96
3	Nano-NiFe ₂ O ₄ @TiO ₂ -ILPip ²⁰	20 mg	PEG-400, 80 °C	10	97
4	L-Proline ²¹	10 mol%	$H_2O: EtOH (1:1), 80 \ ^{\circ}C$	600-720	89
5	$\operatorname{ZrCl}_{4}^{22}$	20 mol%	Solvent-free, 80 °C	300	86
6	APTES-MNPs ²³	10 mol%	Solvent-free, 100 °C	15	93
7	$[H_3N^+CH_2CH_2OH][CH_3COO^-]^{24}$	10 mol%	EtOH, r.t.	720	94
8	β-Cyclodextrin ²⁶	20 mol%	H ₂ O: EtOH (4:1), 80–100 °C	150	93
9	STA-amine-Si-magnetite ²⁷	10 mg	MeOH, 60 °C	27	96.6
10	[Bu ₃ NH][HSO ₄] ²⁸	20 mol%	Solvent-free, 80 °C	9	94
11	[bmim]OH ²⁹	10 mol%	EtOH, 60 °C	60	97
12	CAN ³⁰	5 mol%	PEG-400, 45 °C	50	90
13	InCl ₃ ³¹	20 mol%	Solvent-free, 80 °C	25	94
14	[Bn-DBU][TFA]	28 mol%	Solvent-free, 100 °C	8	90

tolerate a wider range of substrates in comparison with Brønsted acidic or basic ILs (entries 10 and 11). Therefore, these merits tend to introduce [Bn-DBU][TFA] as an alternative to already existing catalysts for the synthesis of **4**.

An important feature of this protocol is that the catalyst can be easily separated from the reaction mixture. At the end of the model reaction, performed under the optimized conditions, water was added to the reaction mixture and the IL was separated from the solid product by decantation of the supernatant aqueous solution. The aqueous extract was then evaporated under vacuum and the remaining IL was collected for reuse in the next cycle of the trial reaction using appropriate amounts of the reactants. It is interesting to note that the IL can be recycled at least four times without appreciable loss of its activity (Fig. 2).

The IR spectrum of [Bn-DBU][TFA] after the 4th recycling is almost identical to that of the fresh IL and this means that it remains intact during use in the synthesis of **4h** (Fig. 3).

Nearly identical spectra were also obtained by energydispersive X-ray (EDX) analysis of these two samples (Fig. 4). The slight differences that are seen between the intensities of the peaks in the resulting EDX spectra can be attributed to the



Fig. 2 Reusability tests for [Bn-DBU][TFA] in terms of yield and reaction time of the model reaction.







Fig. 4 The EDX spectra of fresh [Bn-DBU][TFA] and after the 4th recycling in the synthesis of $\mathbf{4h}$.

error of EDX analysis and to the minute contamination of the recycled sample (see S4 of the ESI[†]).

Conclusions

The two ionic liquids denoted here as [Bn-DBU][AcO] and [Bn-DBU][TFA] were prepared by benzylation of DBU and anion exchange of the resulting salt with AcO⁻ and trifluoroacetate (TFA⁻), respectively. These ionic liquids show significant catalytic efficiencies in the synthesis of 3-amino-5,10-dioxo-1-aryl-5,10dihydro-1H-pyrazolo[1,2-b]phthalazin-2-carbonitriles from the domino reaction of phthalhydrazide, arylaldehyde, and malononitrile/ethyl cyanoacetate. DFT calculations at the B3LYP/SVP level of theory based on the mechanism generally proposed for this reaction are in agreement with the catalytic efficiency of these two ionic liquids and the supremacy of [Bn-DBU][TFA]. These unprecedented calculations show that two transition states can be postulated for this reaction whose energies are considerably decreased by the ionic liquids. Moreover, the transition states are not affected similarly and symmetrically by the two ionic liquids and this results in different energy profiles for the reaction in the two ionic liquids. However, although the energy profiles correspond to pre-equilibrium kinetics for the reaction in [Bn-DBU][OAc], they introduce the first reaction step as the rate limiting step for the reaction in [Bn-DBU][TFA]. In addition, the energy profiles display a slightly lower activation energy for the reaction in [Bn-DBU][TFA], which accounts for its slightly higher rate in comparison with the reaction in [Bn-DBU][AcO]. These agreements between the DFT calculations and the experimental data lend substantial credits to the proposed mechanism. This reaction is very similar to the synthesis of many other heterocycles. Thus, the results can help us to understand the mechanism and therefore the limits of the relevant syntheses. The present study also shows that the slight difference between the catalytic activities of the two ionic liquids comes from their differences in ionic bond strength and orientation of their anions. Due to these differences, the ionic liquids affected the kinetics of the reaction differently. [Bn-DBU][TFA], as the better ionic catalyst, can be easily separated from the reaction mixtures and can be reused several times without significant decrease in its catalytic activity. Overall, a catalyst ion (like TFA) should have a weak ionic bond with its counter ion in an IL to assemble a low-energy TS with the substrates. TFA in addition to possessing this character is a carboxylate ion with the ability to mediate a proton transfer by the aid of its π -system in a rate determining TS of the reaction. We anticipate that these facts will help chemists to organize the design of ILs and redirect the current efforts on unsystematic functionalization and use of ILs as simple bases or acids.

Experimental

Materials and methods

All the chemicals were purchased from Merck or Aldrich chemical companies. The products were identified by comparison of their melting points and spectral data with those of the authentic samples prepared independently by the previously reported methods. Melting points were determined using a Kofler hot stage apparatus and are uncorrected. Monitoring of the reactions was performed by TLC on silica gel (polygram SILG/UV 254) plates. The Fourier transform infrared (FT-IR) spectra were obtained by using KBr discs on a PerkinElmer Spectrum One apparatus in the range of 400–4000 cm⁻¹. The ¹H NMR (400 MHz) spectra were recorded on a Bruker-AVANCE spectrometer and the chemical shifts were measured with respect to the deuterated solvent. Water contents of the ILs were measured by using Karl Fischer titration (Metrohm 890 Titrando).

Synthesis of [Bn-DBU][OAc] and [Bn-DBU][TFA] ILs

The ionic liquids were prepared via anion exchange from the pre-synthesized [Bn-DBU]Cl salt.49 To synthesize the [Bn-DBU]Cl salt, DBU (50 mmol, 7.6 g) and benzyl chloride (80 mmol, 10.1 g) were added to a flask (100 mL) containing ethyl acetate (50 mL) and a magnetic stirring bar. The reaction mixture was stirred at room temperature for 48 h, during which the solution turns into two separate liquid phases. The supernatant ethyl acetate phase was separated off and the remaining pasty solid was washed with diethyl ether $(3 \times 4 \text{ mL})$ to remove the unreacted starting materials. The residual solvent was evaporated under vacuum and the remaining salt [Bn-DBU]Cl was collected. To derive the desirable ILs, [Bn-DBU]Cl (30 mmol, 8.3 g) and a slight excess amount (35 mmol) of NaY (Y_1 = OAc 4.8 g and Y_2 = TFA ($CF_3CO_2^-$) 2.9 g) was added to acetonitrile (60 mL) in a canonical flask (100 mL) containing a magnetic stirring bar. The mixture was stirred at room temperature for about 48 h. The solid (excess NaY and NaCl) was removed by centrifugation and the liquid phase was heated at 80 °C in vacuo to evaporate acetonitrile and volatile impurities. Accordingly, the ILs, [Bn-DBU][OAc] and [Bn-DBU] [TFA], were prepared in 92% and 94% yields, respectively (Scheme 1). The optimized structures of [Bn-DBU][OAc] and [Bn-DBU][TFA] ILs at the B3LYP/SVP level of theory in the gas phase are given in Fig. S1 of the ESI.[†] The water contents of [Bn-DBU][TFA] and [Bn-DBU][OAc] were measured by Karl Fischer titration to be 11.13% and 1.10%, respectively.

Spectroscopic characterization of the ILs

For the FT-IR and ¹H NMR spectra of the synthesized ILs see Fig. S2 and S3 in the ESI.†

Selected data for [Bn-DBU][OAc]. Pale yellow oil; ¹H NMR (D₂O, 400.13 MHz) $\delta_{\rm H}$ 7.35 (2H, t, *J* 7.2 Hz, Ar–H), 7.29 (1H, t, *J* 7.2 Hz, Ar–H), 7.17 (2H, d, *J* 7.2 Hz, Ar–H), 4.50 (2H, br s, CH₂), 3.55 (2H, br s, CH₂), 3.47–3.39 (4H, m, 2 CH₂), 2.71–2.69 (2H, m, CH₂), 2.01–1.99 (2H, m, CH₂), 1.87 (3H, br s, CH₃), 1.60 (4H, br s, 2 CH₂), 1.44 (2H, br s, CH₂); FT-IR (KBr, cm⁻¹): 2935, 2861, 1645, 1620, 1527, 1496, 1325.

Selected data for [Bn-DBU][TFA]. Pale yellow oil; ¹H NMR (D₂O, 500 MHz) $\delta_{\rm H}$ 7.45 (2H, t, *J* 7.3 Hz, Ar–H), 7.39 (1H, t, *J* 7.1 Hz, Ar–H), 7.27 (2H, d, *J* 7.3 Hz, Ar–H), 4.45 (2H, br s, CH₂), 3.57–3.48 (6H, m, 3 CH₂), 2.82–2.80 (2H, m, CH₂), 2.11–2.08 (2H, m, CH₂), 1.70 (4H, br s, 2 CH₂), 1.53 (2H, br s, CH₂);

General procedure for the synthesis of 1*H*-pyrazolo[1,2-*b*]-phthalazine-5,10-diones

To a mixture of an aromatic aldehyde (1 mmol), malononitrile (1 mmol, 0.066 g) or ethyl cyanoacetate (1 mmol, 0.113 g), and phthalhydrazide (1 mmol, 0.162 g) was added the Bn-DBUbased ionic liquid (0.28 mmol, 0.085 g of [Bn-DBU][OAc] or 0.10 g of [Bn-DBU][TFA]). The mixture was stirred at 100 °C and progress of the reaction was monitored by TLC using *n*-hexane and ethyl acetate (in the ratio of 2:1) as an eluent. After completion of the reaction, according to the times specified in Table 1, the mixture was cooled at room temperature and to this, while stirring, was added distilled water (6 mL). The solid crude product, which precipitated at this end, was separated by decantation of the supernatant aqueous solution and then recrystallized from hot ethanol (95%). The aqueous solutions of several experiments were combined and evaporated at 60 °C under vacuum. The dried IL was collected and stored until reuse in the next cycle of the same synthesis.

Conflicts of interest

There are no conflicts of interest to declare.

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